7. (Twice Amended) The method of claim 6 wherein said protein which induces the formation of tendon or ligament tissue is selected from the group consisting of BMP-12, BMP-13, and MP52.

14. (Twice Amended) The composition of claim 8 wherein said protein which induces the formation of tendon or ligament-like tissue is selected from the group consisting of BMP-12, BMP-13, and MP52.

REMARKS

Claims 7 and 14 are amended to render the language of the claims more precise. Claims 1, 6-8, 10, 13-14, 16-17, and 19-21 are pending in the application. Attached is an appendix containing a version of the claims showing changes made by these amendments. For the convenience of the Examiner, a clean set of pending claims is also attached.

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 1, 6-8, 10, 13-14, 16-17, and 19-21 in condition for allowance. Applicants submit that the proposed amendments to claims 7 and 14 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner. Applicants further submit that entry of the amendment would place the application in better form for appeal, should the Examiner maintain the rejections of the pending claims.

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REJECTION UNDER 35 U.S.C. § 112

The Examiner rejected claims 7 and 14 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. The Examiner specifically objects to the language "BMP-12 and members of the BMP-12 subfamily" as double inclusion. Claims 7 and 14 have been amended to remove this language, rendering the claims sufficiently precise to meet the requirements of 35 U.S.C. § 112, 2nd paragraph. Thus, Applicants request that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 103

Claims 1, 6-8, 10, 13-14, 16-17, and 19-21 are rejected as allegedly obvious over United States Patent No. 5,700,774 (Hattersley) in view of United States Patent No. 5,713,374 (Pachence). The Examiner states that Hattersley teaches a method and composition for repairing, reducing, or preventing damage to cartilage and cartilaginous tissue comprising administering a BMP together with PTHrP (parathyroid hormone recombinant peptide). The Examiner contends that it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention by combining the teachings of Hattersley with Pachence, which describes a method for anchoring tissue grafts into a cartilage defect. According to the Examiner, a motivation to combine the two references is the teaching in Pachence that osteochondral grafts or chondrocytes can be utilized for articular cartilage repair and/or regeneration. Applicants respectfully disagree with the Examiner's arguments.

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First, there is no motivation to combine the teachings of Hattersley and Pachence. The Examiner states "In-so-far-as Hattersley does not teach osteochondral graft, Pachence teaches a method to repair articular cartilage/regeneration which utilizes transplantation of osteochondral grafts and chondrocytes." This combination would require impermissible hindsight. Hattersley describes cartilage repair by administering growth factors. Hattersley does not provide any reason why one would want to or need to use an osteochondral graft for this purpose. Applicants note here that there are significant differences between cartilage grafts and osteochondral grafts, and enclose Miller, M., *Atlas of Chondral Injury Treatment*. Operative Techniques in Orthopaedics 7(4) 289-293 (1997) to demonstrate this point (see page 291). Pachence mentions that osteochondral grafts may be used for cartilage repair, but fails to provide any indication that these grafts would be suitable for use with a growth factor, let alone BMPs. It is only with the pending specification that one skilled in the art would know how to treat these grafts with BMPs and administer them to a patient. Therefore, it is only with impermissible hindsight that one skilled in the art could combine the teachings of Hattersley and Pachence to arrive at the claimed invention.

Even if a motivation to combine the reference exists, the combination of Hattersley and Pachence does not render the instant claims obvious. Hattersley teaches the use of BMPs in combination with PTH to induce cartilage regeneration. At best, a combination of the teachings of Hattersley and Pachence would produce grafts treated with both BMPs and PTH. Neither Hattersley nor Pachence provides any motivation whatsoever to remove an element, which Hattersley defines as an essential

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factor in chondrocyte development and maturation, from this combination to achieve the claimed invention.[1] (See, Hattersley, Col. 1, line 66 - Col. 2, line 6.)

It is well accepted that the omission of an element and retention of its function is an indication of unobviousness. *In re Edge*, 359 F.2d 896 (CCPA 1966); Manual for Patent Examining Procesure (2144.04). Hattersley does not teach or even suggest that BMPs alone could be used to induce cartilage regeneration. As a result, Hattersley teaches away from the instant invention by indicating that PTH would be required in any composition comprising a BMP for the induction of cartilage regeneration.

In response to Applicants' previous arguments on this issue, the Examiner states that it is evident from Hattersley that the key ingredient is BMP (Office Action of June 17, 2002, page 8, lines 8-10). Applicants respectfully disagree with this characterization.

Contrary to the Examiner's contention, Hattersley makes it quite clear that PTH is a key ingredient of all compositions disclosed in the specification. Hattersley does not suggest that any of the various BMPs mentioned in the patent can be used without PTH for the regeneration of cartilage. In fact, Hattersley goes out of the way to specify that both BMP and PTH must be present in the methods and compositions described. See e.g., Col. 4, lines 26-30 ("The methods and compositions of the present invention may comprise simultaneous or sequential administration *of at least two active* agents, a TGF-β protein and a parathyroid hormone-related peptide, to a patient or site in need of cartilage repair, formation or manintenance.") (emphasis added). In view of this

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[1] Hattersley also teaches that chondrocytes are the tissue source for cartilage development.

disclosure, one of skill in the art would understand Hattersley to teach that PTH is as least as essential as BMP in the disclosed compositions.

It is only with hindsight and the instant specification that one skilled in the art would understand the relative importance of PTH and BMPs in the claimed methods. It is well established that employing such hindsight to reach a finding of obviousness is impermissible. Upon reading Hattersley, one would only know that is PTH an essential element in methods and compositions for the regeneration of cartilage. It is only with Applicants' disclosure that a skilled artisan would consider the feasibility of regenerating articular cartilage by administration of an osteochondral graft treated with a bone morphogenetic protein—in the absence of PTH—as is claimed by Applicants.

Accordingly, Applicant's request that the rejection under 35 U.S.C. §103(a) be withdrawn.

In view of the foregoing remarks, Applicants submit that this claimed invention, as amended, is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

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(Hattersley, Col. 5.)

PATENT
Customer No. 22,852
Attorney Docket No. 08702.0068-00000

Respectfully submitted,

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Dated: July 17, 2003

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Claims with Markings to Show Changes

7. (Twice Amended) The method of claim 6 wherein said protein which induces the formation of tendon or ligament tissue is selected from the group consisting of BMP-12, BMP-13, [~~members of the BMP-12 subfamily,~~] and MP52.

14. (Twice Amended) The composition of claim 8 wherein said protein which induces the formation of tendon or ligament-like tissue is selected from the group consisting of BMP-12, BMP-13, [~~members of the BMP-12 subfamily,~~] and MP52.

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Clean Set of Pending Claims

1. A method for regeneration of articular cartilage comprising administering to an area in need of regeneration of said articular cartilage an osteochondral graft having applied thereto an amount of at least one purified bone morphogenetic protein (BMP) effective for the regeneration of said articular cartilage.

6. The method of claim 1 further comprising a protein which induces the formation of tendon or ligament tissue.

7. The method of claim 6 wherein said protein which induces the formation of tendon or ligament tissue is selected from the group consisting of BMP-12, BMP-13, and MP52.

8. A composition for regeneration of articular cartilage comprising an osteochondral graft having applied thereto an amount of at least one purified bone morphogenetic protein (BMP) effective for the regeneration of said articular cartilage.

10. The composition of claim 8 wherein said BMP is BMP-2.

13. The composition of claim 8 further comprising a protein which induces the formation of tendon or ligament-like tissue.

14. The composition of claim 8 wherein said protein which induces the formation of tendon or ligament-like tissue is selected from the group consisting of BMP-12, BMP-13, and MP52.

16. The method of claim 1 wherein said osteochondral graft is osteochondral allograft.

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17. The method of claim 1 wherein said osteochondral graft is osteochondral autograft.

19. The composition of claim 8 wherein said osteochondral graft is osteochondral allograft.

20. The composition of claim 8 wherein said osteochondral graft is osteochondral autograft.

21. A composition for the regeneration of articular cartilage said composition comprising an osteochondral graft having applied thereto an amount of BMP-2 effective for the regeneration of said articular cartilage.

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